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Evidence for Linkage of Charcot-Marie-Tooth Neuropathy to the Duffy Locus on Chromosome 1

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SUMMARY

A linkage study was performed on three families with classic Charcot-Marie-Tooth (CMT) hereditary neuropathy with clinical manifestations of autosomal dominant inheritance, distal muscle weakness and atrophy, hyporeflexia, and slow motor nerve conduction velocities. Two families comprising 3 and 4 generations and a total of 23 affected persons were informative for the Duffy locus known to be on the long arm of chromosome 1. The maximum total lod score was 2.297 at recombination fraction $\theta = .1$. The third family was informative for PGM_1 (on the short arm of chromosome 1). There was no evidence for linkage of CMT to PGM_1 in this third family, but only values of θ less than .03 could be excluded. There was no evidence for linkage of CMT to seven other informative markers in these families. We conclude that the gene controlling the occurrence of dominant CMT may be approximately 10 centimorgans from the Duffy locus on the long arm of chromosome 1. Additional studies are required to confirm these findings.

INTRODUCTION

Charcot-Marie-Tooth (CMT) disease is a hereditary neuropathy first described in 1886. The classic form of the disease includes autosomal dominant inheritance,

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juvenile or young adult onset of distal muscle weakness and atrophy, depressed tendon reflexes, high arched feet with foot drop, and slow motor nerve conduction velocities. In 1978, Heimler et al. reported a single family with a dominant hereditary neuropathy that seemed to be segregating together with the dominant nevoid basal cell carcinoma syndrome [1]. Because of previous evidence that the nevoid basal cell carcinoma syndrome might be linked to the Rh blood group locus on chromosome 1, the authors speculated that the locus for CMT syndrome could also be on the first chromosome. Reported here are the results of the first detailed linkage analysis of three families with the dominant CMT syndrome. (An abstract of this material has appeared previously [2].)

PATIENTS AND METHODS

We selected three families with classic autosomal dominant CMT syndrome. Diagnosis of affected individuals was by neurologic examination and motor nerve conduction velocity studies as outlined by Bird and Kraft [3]. Affected members had hypoactive tendon reflexes, distal muscle weakness and atrophy, and slow motor nerve conduction velocities (less than 20 meters/sec in at least one family member). Affected members in family C had enlarged peripheral nerves to palpation, and one affected member from both families A and B had sural nerve biopsies demonstrating hypertrophic change. Family A (fig. 1) had eight affected individuals in 4 generations. Family B (fig. 2) had 15 affected individuals in 3 generations. Family C (fig. 3) had six affected individuals in 2 generations. All the clinical evidence supports the hypothesis that these three families have the same disease, although there is no biochemical marker for CMT.

The affected and unaffected individuals in these three families including appropriate spouses were evaluated for the following 25 blood markers: ABO, Rh, Kell, Duffy, P, MNS, Hgb, AcP, GLO, NP, ADA, 6PGD, PGM_1, PGM_2, PGM_3, AK, Eno-1, GOT, GPT, UMPK,

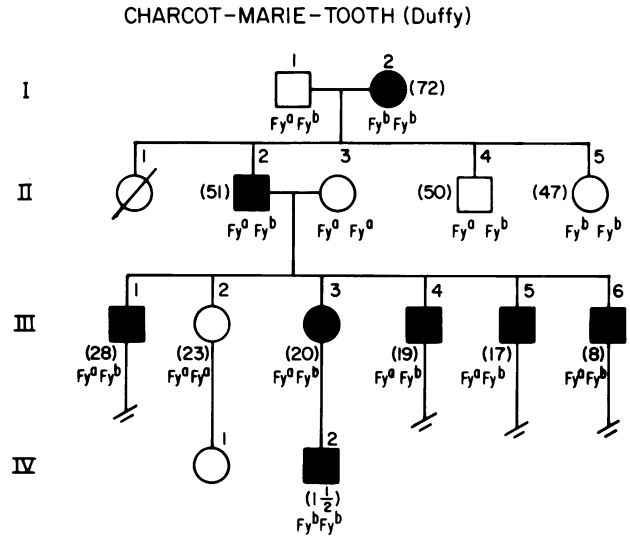

FIG. 1.—Pedigree of family A with CMT showing Duffy blood group typing. Persons with CMT are in *black* and ages are in *parentheses*.

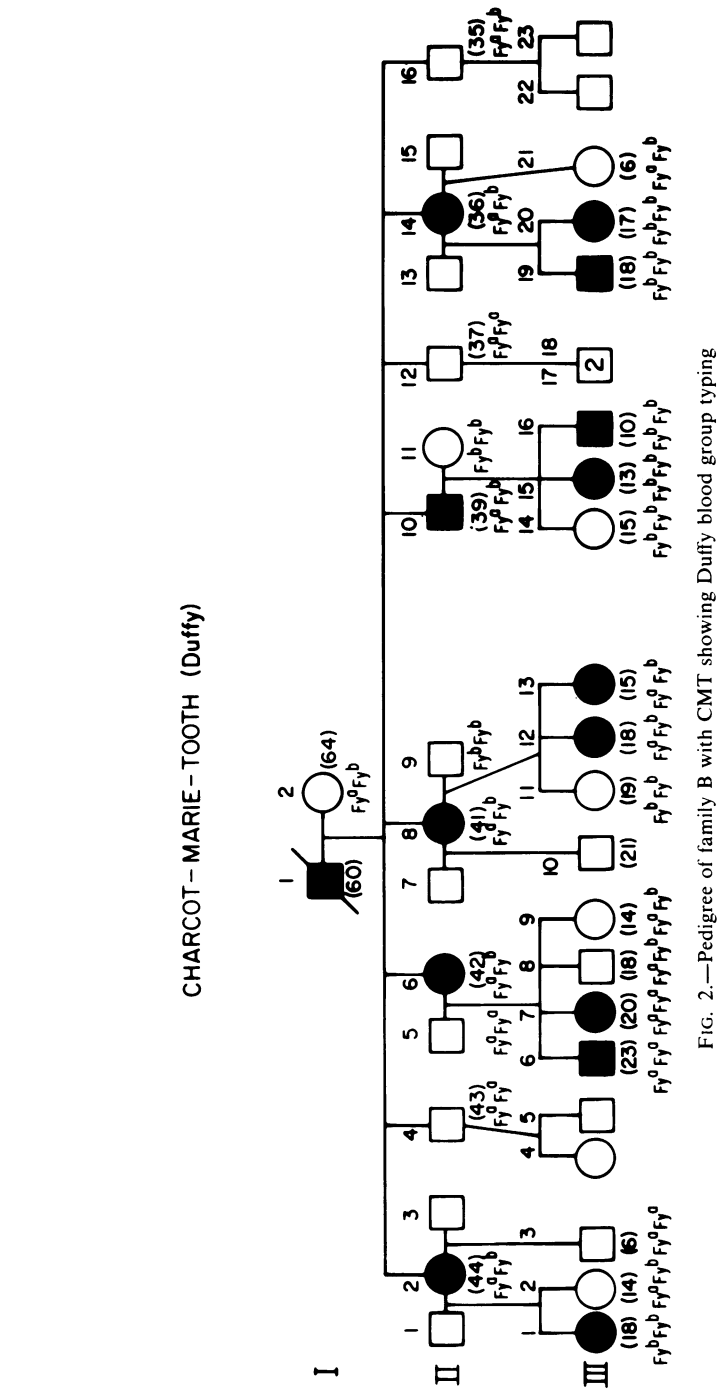

FIG. 2.—Pedigree of family B with CMT showing Duffy blood group typing

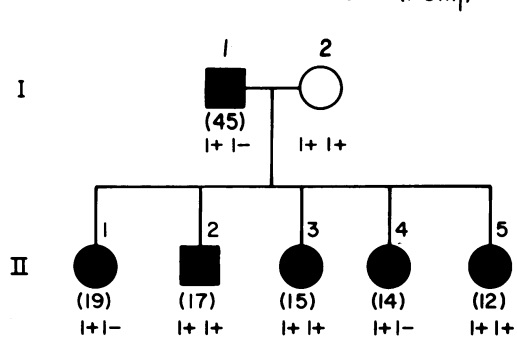

FIG. 3.—Pedigree of family C with CMT showing PGM_1 typing. PGM_1 alleles designated according to Sutton and Burgess [6].

ESD, Bf(GBG), C2, C6, and Gc. Lod scores were computed with the LIPED computer program of Ott [4]. The separation of male and female lods was carried out by a method of Morton [5]. PGM_1 was biochemically analyzed by the method of Sutton and Burgess [6].

RESULTS

Family A (fig. 1) was informative for the Duffy blood group locus on the long arm of chromosome 1. At the Duffy locus, there are two common alleles in the white population, designated Fy^a and Fy^b as shown on the family pedigree. Family A had eight affected persons in 4 generations. The youngest person at risk was over the age of 20, and the diagnosis of CMT has been made in a 1½-year-old boy in the fourth generation. Analyzing this pedigree for CMT and Duffy, the highest lod score for the combined sexes is 2.107 at zero recombination (table 1). The two informative matings are both phase known double backcrosses, one with a male and one with a female informative parent, so that the lods can be separated naturally according to the two sexes.

Family B also showed positive but weak evidence for linkage of CMT to Duffy with highest lod scores of 1.404 at $\theta = 0$ for females and of .357 at $\theta = .3$ for the combined sexes (table 2). These numbers reflect the fact that two at-risk but clinically normal children in the youngest generation were initially excluded from the data because they were under age 10 (III-3 and III-21, fig. 2). Previous studies requiring further clarification have suggested that penetrance of the CMT gene may not be complete until after the first decade of life [3]. However, it is instructive to compute the lod scores with these two children included and considered unaffected. In support of this line of reasoning, we note that both children have normal neurological examinations and, most important, normal motor nerve conduction velocities. Although possible, there has never been a report of such carefully studied persons later developing the disease. Occurrence of the complete CMT syndrome in the first decade of life is well documented [7]. Furthermore, of the 17 offspring at risk for CMT in the youngest generation of this family, nine are clearly affected, thus already achieving the expected 50% affected ratio. With

TABLE 1

CMT (FAMILY A)

	$\theta = 0$	.1	.2	.3	.4
Male lod scores	1.806	1.532	1.225	.877	.475
Female lod scores	.301	.255	.204	.146	.079
Total	2.107	1.787	1.429	1.023	.554

these two presumably unaffected children included in the data, there is further support for linkage of CMT to Duffy (table 2). For females at zero recombination fraction, the lod score is 1.95. However, it is only .53 at $\theta = .2$ for the combined sexes. The unusual male/female difference in recombination may simply reflect the small number of individuals studied.

When the data for CMT and Duffy for families A and B (III-3 and III-21 in family B considered unaffected) are combined, the highest lod score is 2.297 at $\theta = .10$, suggesting, but not proving, linkage of these two loci (table 3).

Families A and B were also informative for a total of seven additional markers, none of which showed evidence for linkage (table 4). Linkage could be excluded for C6 and MNSs ($\theta = .1$) by the criterion of lod score $Z < -2$. (Chromosome assignments for these additional informative markers are: AcP, no. 2; GLO, no. 6; C6, ?; MNSs, no. 4; ABO, no. 9; GPT, no. 10; P, ?. The other markers tested were not informative.)

Chromosome karyotypes were performed on an affected individual from both families A and B. No heteromorphisms were found for chromosome 1 (such as the uncoiler locus) that might have provided an additional marker for linkage studies.

In family C (fig. 3), there was an affected father and five affected children (phase unknown double backcross). The father was informative for the PGM_1 locus assigned to the short arm of chromosome 1. Depending on the phase, two or three recombinations out of five opportunities occur between CMT and PGM_1 in this pedigree, making close linkage unlikely. Because of small numbers, only recombination values of less than .03 could be excluded by the criterion of a lod score $Z < -2$. Family C was not informative for Duffy.

TABLE 2

CMT AND DUFFY (FAMILY B)

	$\theta = 0$	.1	.2	.3	.4
(a) Male lod scores*	$-\infty$	−1.110	−.470	−.189	−.047
(b) Male lod scores†	$-\infty$	−.905	−.328	−.117	−.029
(a) Female lod scores*	1.404	1.052	.783	.546	.284
(b) Female lod scores†	1.954	1.415	.859	.395	.144
(a) Total*	$-\infty$	−.058	.313	.357	.237
(b) Total†	$-\infty$	.510	.531	.278	.115

* Two young children at risk not included.
† Two young children at risk included as unaffected.

TABLE 3

CMT (COMBINED FAMILIES A AND B)

	$\theta = 0$	.1	.2	.3	.4
Male lod scores	$-\infty$	.627	.897	.760	.446
Female lod scores	2.255	1.670	1.063	.541	.223
Total	$-\infty$	2.297	1.960	1.301	.669

DISCUSSION

Linkage studies of dominant diseases have the potential for providing two important benefits for clinical medicine. First, they can clarify nosology. Disorders that appear similar clinically may be shown to be the result of mutations at different loci. Conversely, diseases that appear different clinically may be shown to be the result of mutations at the same loci. Secondly, close linkage of a disease to a readily available marker may assist in the pre- or postnatal diagnosis of individuals at risk. Two examples of autosomal dominant neurologic diseases that have been shown to fall within specific linkage groups are the linkage of myotonic muscular dystrophy to the secretor locus [8] and the linkage of one form of hereditary ataxia to the *HLA* locus on chromosome 6 [9].

Our study shows evidence for linkage of classic Charcot-Marie-Tooth hereditary neuropathy to the Duffy blood group locus. The most recent map of chromosome

TABLE 4

CMT—LOD SCORES OF MARKERS SHOWING NO EVIDENCE FOR LINKAGE

	$\theta = 0$	.1	.2	.3	.4
AcP:					
Family A	.602	.470	.338	.211	096
Family B	$-\infty$	−1.105	−.218	.042	.051
Combined A + B	$-\infty$	−.635	.120	.253	.147
GLO:					
Family A	$-\infty$	.532	.526	.360	.131
Family B	$-\infty$	−1.925	−.681	−.140	.056
Combined A + B	$-\infty$	−1.393	−.155	.220	.187
C6:					
Family A	$-\infty$	−.212	.046	.053	.011
Family B	$-\infty$	−2.092	−.562	.022	.164
Combined A + B	$-\infty$	−2.304	−.516	.075	.175
MNSs:					
Family A	$-\infty$	−1.775	−.775	−.303	−.071
Family B	$-\infty$	−2.886	−1.147	−.359	−.022
Combined A + B	$-\infty$	−4.661	−1.922	−.662	−.093
ABO:					
Family A	$-\infty$	−.121	−.003	.010	.003
Family B	$-\infty$	−.965	−.337	−.094	−.010
Combined A + B	$-\infty$	−1.086	−.340	−.084	−.007
GPT:					
Family A	$-\infty$	−.887	−.388	−.151	−.035
P:					
Family A	.250	.175	.107	.051	.013

1 taken from Rao et al. places the Duffy locus on the long arm near the centromere [10]. The lod score of 2.297 at $\theta = .10$ found in our study is suggestive but by no means definitive evidence that CMT and Duffy are linked. The odds in favor of linkage are approximately 200 to one. A lod score of 3.0 or higher would provide more conclusive evidence for linkage. However, the present finding is of sufficient interest to stimulate the investigation of additional families and markers to extend and clarify these results. It should be kept in mind that not all families with dominant hereditary neuropathy will necessarily have the same disease or mutation. Therefore, many generations of single families must be studied as well as larger numbers of separate families.

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REFERENCES

1. Heimler A, Friedman E, Rosenthal AD: Naevoid basal cell carcinoma syndrome and Charcot-Marie-Tooth disease. *J Med Genet* 15:288–291, 1978
2. Bird TD, Ott J, Giblett ER: Linkage of Charcot-Marie-Tooth neuropathy to the Duffy locus on chromosome 1. *American Society of Human Genetics, Abstracts of 31st Annual Meeting*, New York, Sept. 1980, p 99A (#300) and *Am J Hum Genet* 32:99A, 1980
3. Bird TD, Kraft GH: Charcot-Marie-Tooth disease: data for genetic counseling relating age to risk. *Clin Genet* 14:43–49, 1978
4. Ott J: Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. *Am J Hum Genet* 26:588–597, 1974
5. Morton NE: Analysis of crossing over in man, in *Human Gene Mapping, 4(1977), Birth Defects: Orig Art Ser*, XIV(4), New York, The National Foundation, 1978
6. Sutton JG, Burgess R: Genetic evidence for four common alleles at the phosphoglucomutase-1 locus (PGM_1) detectable by isoelectric focusing. *Vox Sang* 34:97–103, 1978
7. Vanasse M, Dubowitz V: Dominantly inherited peroneal muscular atrophy (HMSN type 1) in infancy and childhood. *Muscle Nerve* 4:26–30, 1981
8. Harper PS, Rivas ML, Bias WB, Hutchinson JR, Dyken PR, McKusick VA: Genetic linkage confirmed between the locus for myotonic dystrophy and the ABH-secretion and Lutheran blood group loci. *Am J Hum Genet* 24:310–316, 1972
9. Morton NE, Lalouel JF, Hackson RD, Yee S: Linkage studies in spinocerebellar ataxia (SCA). *Am J Med Genet* 6:251–257, 1980
10. Rao DC, Keats BJ, Lalouel JM, Morton NE, Yee S: A maximum-likelihood map of chromosome 1. *Am J Hum Genet* 31:680–696, 1979